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<p>(54) Title: RING-SHAPED DEVICES</p> <p>(57) Abstract</p> <p>The invention relates to a ring-shaped device comprising: (a) a first compartment comprising an non-medicated core of ethylene-vinylacetate copolymer, encircled by a steroid hormone loaded ethylen-vinylacetate copolymer layer, and a non-medicated outer layer of ethylene-vinylacetate copolymer, (b) a second compartment comprising a core of ethylene-vinylacetate copolymer loaded with a steroid hormone and a non-medicated outer layer of ethylene-vinylacetate polymer, and (c) optionally placebo segments of a thermo-plastic material separating the first from the second compartment. In a preferred embodiment the invention is related to a two-compartment vaginal ring, the first compartment comprising crystalline etonogestrel and the second compartment comprising a (sub)-saturated mixture of etonogestrel and ethinyl estradiol, both compartments optionally being separated from each other by placebo segments of high density polyethylene.</p>			

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## RING-SHAPED DEVICES

5 The invention relates to ring-shaped devices and to a method of manufacture the same.

The invention relates in particular to ring-shaped vaginal devices, i.e. to vaginal rings.

Ring-shaped devices, and especially vaginal rings, are well known in the art. A two-layered 10 one-compartment vaginal ring, for example, is disclosed in USP 4,237,885, in which a drug (progestational or estrogenic steroid) on a carrier is encircled by a polymeric tube, consisting of an ethylene-vinylacetate copolymer, both ends of which are joined together with a solid polymeric plug. Devices of this type, however, do not provide acceptable release patterns.

Improvement was sought by using other shapes or other materials. A two-layered one-15 compartment vaginal ring made from silicone elastomer has been disclosed in EP 0,050,867, which ring comprises a silicone elastomer core loaded with active substance surrounded by a non-loaded silicone elastomer layer, which consists of two different compositions.

Another improvement was claimed in US Patent 4,292,965, which disclosed a three-layered one-compartment ring. This ring comprises an inert silicone elastomer core encircled by a 20 medicated silicone layer, and a non-medicated silicone outer layer.

These above-mentioned one-compartment rings have the disadvantage that, when loaded with more than one active substance, release patterns of these substances can not be adjusted independently. Such devices usually show sub-optimum release patterns for the different substances, whereas it is generally preferred that all substances are released in a controlled rate 25 and during a similar duration of time. As a consequence the release ratio of the active substances undergoes a change after a period of time.

In an attempt to solve these problems a two-compartment vaginal ring has been disclosed in US 30 Patent 4,596,576. This device comprises two two-layered compartments, each containing another active substance. An advantage of this device is that the release ratio can be changed by changing the lengths of the compartments. To achieve a suitable ring with a constant release ratio, it is however necessary to join the ends of the compartments by using inert stoppers, which completely prevent mixing of the active ingredients. One of the disadvantages of this device is the expensive and difficult method to join the compartment ends to the stoppers, 35 which method can hardly be automated.

Apart from unfavourable release patterns, changing release ratios, and burst effects (excessive release in the first few days), which are frequently occurring with the known vaginal rings, most vaginal rings are prepared from silicone elastomer, which material is nowadays 5 considered as less safe.

It is an objective of the present invention to provide a safe ring-shaped device, with a good release pattern, preventing the disadvantages of the known vaginal rings, and which can be manufactured in a simple automated manner. Another objective of the invention is to provide a 10 ring-shaped device which, after introduction thereof into the vagina, releases the steroid hormones within a short time, preferably within one to two days, to reach the desired plasma levels.

- 15 15 It has been found that a ring-shaped device comprising:
  - (a) a first compartment comprising a non-medicated core of ethylene-vinylacetate copolymer, encircled by a steroid hormone loaded ethylene-vinylacetate copolymer middle layer, and a non-medicated outer layer of ethylene-vinylacetate copolymer;
  - (b) a second compartment comprising a core of ethylene-vinylacetate copolymer loaded with a 20 steroid hormone and a non-medicated outer layer of ethylene-vinylacetate copolymer; and
  - (c) optionally placebo segments of a thermo-plastic material separating the first from the second compartment,fulfils these requirements.
- 25 25 The ring-shaped device according to the invention, is preferably a vaginal ring which can be used for hormone replacement therapy (HRT) or contraception.

The ethylene-vinylacetate copolymer can be any commercially available ethylene-vinylacetate copolymer, for instance as available under the trade names Elvax®, Evatane®, Lupolen V®, 30 Movriton®, Ultrathene®, and Vestypar®.

The thermo-plastic material of the placebo segments can be any thermo-plastic material suitable for pharmaceutical use, such as polypropylene; low, linear low, or very low density polyethylene; ethylene-vinylacetate copolymer, and, preferably, high density polyethylene, such 35 as commercially available Alathon®, Alkathene®, Baylon V®, Carlona®, Carlona P®, Dow

PE®, Eltex®, Elvax®, Evatane®, Ferlene®, Fortilene®, Hi-fax®, Hostaflex®, Hostalen G®, Hostalen PP®, Lactene®, Lupolen®, Lupolen V®, Lyton®, Moplen®, Movriton®, Novatec®, Novolen®, Pro-fax®, Propathene®, Rigidex®, Stamylan®, Stamylan P®, Stamylex®, Teamex®, Tenite®, Trolen PP®, Typar®, Ultrathene®, VestolenP®, Vestypar®, and Vestolen A®.

Particularly good release patterns are obtained when the ethylene-vinylacetate copolymer middle layer of the first compartment is saturated with the progestogen and the ethylene-vinylacetate copolymer core of the second compartment is loaded with a just saturated, and 10 most preferably with a sub-saturated mixture of the progestogen and the estrogen.

Preferred devices for contraceptive use have a first compartment wherein the steroid hormone is a progestogen and a second compartment wherein the steroid hormone is a mixture of a progestogen and an estrogen. Devices especially intended for HRT may advantageously have a 15 first compartment loaded with a mixture of a progestogen and an estrogen and a second compartment loaded with a progestogen. The progestogens of the first and the second compartment may be the same or may be different.

Typically the ethylene-vinylacetate copolymer middle layer of the first compartment comprises 20 the progestogen (or the mixture of the progestogen and the estrogen) in crystalline form.

The lengths of the compartments of the ring-shaped device are chosen to give the required performance. Ratios of the lengths of the first and second compartment are contemplated to be between 30:1 and 1:30, but usually are between 15:1 and 1:1, and preferably are about 2:1. 25 The lengths of the placebo segments are long enough to prevent excessive mixing of the progestogen of the first compartment with the progestogen and/or estrogen of the second compartment. This is usually attained by applying placebo segments of a length between 0.5 and 70 mm. The necessary length depends on the nature of the thermo-plastic material and its capacity to prevent permeation of the active materials. Most ideally the placebo segment completely 30 prevents mixing, since mixing disturbs the release pattern. In practice, however, some mixing, in particular after a longer period of time, occurs due to diffusion of the active ingredients through the placebo segment from one to the other compartment. Such mixing would ultimately lead to the same load of estrogen in both compartments, which of course is unwanted when the loads are meant to be different. Some minor mixing however, is not completely to be prevented 35 and is allowed to the point that the mixing influences the release of the active ingredients in

such a manner that plasma levels of active ingredients get outside the required values. In practice less than 10% mixing, and preferably less than 5% mixing one month after insertion of the device, is acceptable. Usually a length of the placebo segments being preferably about at least half of the length of the second compartment is sufficient to prevent excessive mixing.

5

The ring-shaped device can be manufactured in any size as required. In practice, however an outer ring diameter of about 53.5 mm, a cross sectional diameter of about 3.5 mm, a length of the first compartment of about 100 to 110 mm, a length of the second compartment of about 10 to 40 mm, and a length of each of the two placebo segments of about 5 to 20 mm, has been

10 proven to be very suitable for all purposes. If no placebo segments are used the length of the first compartment is about 110 and the length of the second compartment is preferably 42-52 mm.

15 The progestogen can be any suitable progestogen, such as desogestrel, etonogestrel (3-ketodesogestrel), levonorgestrel, norgestrel, gestodene, and other compounds with similar progestogenic activity. Preferably the progestogen is etonogestrel. The estrogen can be any suitable estrogen, such as estradiol, estriol, mestranol, and ethinyl estradiol. For contraceptive use ethinyl estradiol is preferred, whereas for HRT estradiol is the preferred estrogen.

20 Using the most preferred ring-shaped device of the invention, the ethylene-vinylacetate copolymer layer of the first compartment is loaded with 5-60 % w/w, and preferably with about 15 % w/w of etonogestrel, and the ethylene-vinylacetate copolymer core of the second compartment is loaded with 0.05-3 % w/w, and preferably about 0.25-0.5 % w/w of etonogestrel and 0.05-5 % w/w, and preferably about 0.75-1.5 % w/w of ethinyl estradiol.

25

The preferred vaginal ring releases at least 90 µg/day of etonogestrel and 10 µg/day of ethinyl estradiol, with an upper limit of 450 µg/day and 100 µg/day respectively during Day 1-3, and 150 µg/day and 20 µg/day respectively during Day 4-21.

30 The ring-shaped devices can be prepared in any suitable manner for the manufacture of vaginal rings. A preferred method of manufacture of the ring-shaped device comprises co-extrusion of the core and the layer(s), medicated or non-medicated as required, of each of the first and second compartments to render a fibre with a medicated middle or core layer, respectively. These fibres are cut into pieces of the required lengths, and the pieces are assembled to the

ring-shaped device in a mould kept at about 40 °C, by injection moulding with high density polyethylene of about 230 °C. The rings are thereafter packed in the usual manner.

Another method of manufacture is a welding technique, for instance the hot-gas welding technique, which is especially suitable when no placebo segments are used. This technique is well known in the art. Basically the hot-gas technique is performed in an apparatus consisting of two moulds which are used to clamp the fibre ends and hold them in line to each other. One mould is static and the other is movable. A movable stop is used to assure that the fibre ends are only sticking out of the mould by about 0.5 mm. The apparatus further comprises a capillary which is used to remove residual polymer. The capillary consists of two identical halves, one of which is mounted on the upper part of a mould and the other is mounted on the lower part of the mould. A hot-air gun is used to melt the fibre ends.

In another embodiment the two ethylene-vinylacetate copolymer fibres, loaded with either etonogestrel or a mixture of etonogestrel and ethinyl estradiol, are melt co-extruded together with the skin-core ethylene-vinylacetate copolymer to render a skin-core fibre. These skin-core fibres are cut into pieces of the required length and assembled to a ring in a mould with two suitable pieces injection moulded high density polyethylene and injection moulded at 230 °C, with a mould temperature of 40 °C. The rings are thereafter sterilised and packed in the usual manner, for instance packed in a sachet consisting of a PET (12 µm)/aluminium (9 µm)/LDPE (40 µm) laminate.

The invention is illustrated by the Figures.

Fig. 1 shows schematically an embodiment of a vaginal ring according to this invention, containing the first compartment (a), the second compartment (b) and two placebo segments (c).

Fig. 2 shows a cross-section along the line A-B of the first compartment.

Fig. 3 shows a cross-section along the line C-D of the second compartment.

Fig. 4 shows a cross-section along the line E-F of a placebo segment.

In these drawings an embodiment of the invention is disclosed. The device is made of three compartments (a), (b), and (c), the first two of which comprise an ethylene-vinylacetate copolymer core (1) and (4) respectively, and the latter is an thermo-plastic placebo segment. In the first compartment (Fig. 2) the core (1) is non-medicated, and it further comprises an ethylene-vinylacetate copolymer middle layer (2) loaded with active ingredient, and an ethylene-

vinylacetate copolymer outer layer (3) which is non-medicated. In Fig. 3 the core (4) is loaded with active ingredient, which core is surrounded by an ethylene-vinylacetate copolymer outer layer (5) which is non-medicated. The placebo segments (Fig. 4) preferably consist of one layer of non-medicated thermo-plastic material (6).

5

The invention is further illustrated by the following examples.

**Example 1**

10 A vaginal ring is composed from two steroid loaded compartments and two placebo segments, having the following composition and dimensions (see Figures):

**first compartment (Fig. 2)**

a three-layered fibre comprising:

15 core (1): Evatane® 1040 VN4; diameter 2.96 mm ;  
middle layer (2) loaded with 15 % w/w of etonogestrel in Evatane® 28-25; thickness 75  $\mu$ m, extruded at 105 °C;  
outer layer (3): Evatane® 1040 VN4; thickness 195  $\mu$ m.  
The steroid loaded mixture and Evatane® 1040 VN4 are co-extruded at 120 °C to form a  
20 trilayer fibre.

**second compartment (Fig. 3)**

a two-layered fibre comprising:

25 core (4): Evatane® 28-25 loaded with 0.5 % w/w of etonogestrel and 1.5 % w/w of ethinyl estradiol (EE); diameter 3.35 mm, extruded at 105 °C;  
outer layer (5): Evatane® 1020 VN3; thickness 75  $\mu$ m.

The steroid loaded mixture and Evatane® 1020 VN3 are co-extruded at 110 °C to form a skin-core fibre.

30 **placebo segments (Fig. 4)**

two placebo segments of 16 mm length each, comprising Stamylex® 9119 (6); diameter 3.5 mm.

35 The trilayer fibre is cut into fibre pieces of 110 mm and the skin-core fibre is cut into fibre pieces of 15 mm. One small and one large fibre piece are joined together to a ring-shaped

device by injection moulding of the two placebo segments (HDPE) at 230 °C, with a mould temperature of 40 °C.

**Example 2**

5

According to the procedure of Example 1, ring-shaped devices were prepared comprising compartments having the following content:

first compartment

10 skin/core: Evatane® 1040 VN4;  
 middle layer: Evatane® 28-25 loaded with etonogestrel;  
 outer diameter 3.5 mm.

Medicated layer load (% w/w)	skin thickness (µm)	medicated layer thickness (µm)	extrusion temp. (°C)
10	230	75	120
15	195	75	120
15	230	75	120
15	265	75	120
15	230	75	145
15	175	75	120
15	195	65	120
15	195	85	120

15

second compartment

core: Evatane® 28-25 loaded with etonogestrel and ethinyl estradiol (EE); outer layer: Evatane® 1020 VN3 or Evatane® 1040 VN4; outer diameter 3.5 mm.

5

medicated layer load etonogestrel (% w/w)	medicated layer load EE (% w/w)	skin thickness ( $\mu$ m)	extrusion temp. (°C)
skin material: Evatane® 1020 VN3			
0.5	1.5	65	105
0.5	1.5	80	105
0.8	1.5	50	105
0.8	1.5	65	105
0.8	1.5	80	105
0.5	1.5	75	105
0.5	1.5	75	103
0.5	1.5	75	115
0.45	1.5	75	110
0.5	1.5	75	110
0.55	1.5	75	110
0.5	1.35	75	110
0.5	1.65	75	110
0.25	0.75	85	110
skin material: Evatane® 1040 VN4			
0.37	1.1	345	120
0.37	1.1	380	110
0.37	1.1	425	110

placebo segments

two placebo segments of 16 mm length each, comprising Stamylex® 9119.

## Example 3

The following first compartments containing etonogestrel were prepared. Medicated layer material is Evatane® 28-25; outer diameter is 3.5 mm.

5

entry	skin/core Evatane®	medicated	skin thickness	medicated	extrusion temp.
		layer load		layer	
		etonogestrel		thickness	
		% w/w	µm	µm	°C
1	1040 VN4	10	230	75	120
2	1040 VN4	15	195	75	120
3	1040 VN4	15	230	75	120
4	1040 VN4	15	265	75	120
5	1040 VN4	15	230	75	145
6	1040 VN4	15	195	65	120
7	1040 VN4	15	195	85	120

The following second compartments containing etonogestrel and ethinyl estradiol (EE) were prepared. Medicated layer material is Evatane® 28-25; outer diameter is 3.5 mm:

entry	skin Evatane®	medicated layer		skin thickness	extrusion temp.
		etono- gestrel	EE		
		% w/w	% w/w		
8	1020 VN3	0.5	1.5	65	105
9	1020 VN3	0.5	1.5	80	105
10	1020 VN3	0.8	1.5	50	105
11	1020 VN3	0.8	1.5	65	105
12	1020 VN3	0.8	1.5	80	105
13	1020 VN3	0.5	1.5	75	105
14	1020 VN3	0.5	1.5	75	103
15	1020 VN3	0.5	1.5	75	115
16	1020 VN3	0.45	1.5	65	110
17	1020 VN3	0.5	1.5	75	110
18	1020 VN3	0.55	1.5	75	110
19	1020 VN3	0.5	1.35	75	110
20	1020 VN3	0.5	1.65	75	110
21	1020 VN3	0.25	0.75	75	120
22	1040 VN4	0.37	1.1	345	120
23	1040 VN4	0.37	1.1	380	110
24	1040 VN4	0.37	1.1	425	110

The following vaginal rings were prepared according to the method of Example 1:

- (a) first compartment of material of entry 6 (110 mm);
- 10 second compartment of material of entry 9 (15 mm);
- placebo segments of Stamylex® 9119 (16 mm).

(b) first compartment of material of entry 7 (110 mm);  
second compartment of material of entry 13 (16 mm);  
placebo segments of Stamylex® 9119 (16 mm).

5 (c) first compartment of material of entry 7 (110 mm);  
second compartment of material of entry 13 (15 mm);  
placebo segments of Stamylex® 9119 (16 mm).

(d) first compartment of material of entry 6 (110 mm);  
10 second compartment of material of entry 21 (20 mm);  
placebo segments of Stamylex® 9119 (15.5 mm).

(e) first compartment of material of entry 6 (110 mm);  
second compartment of material of entry 21 (30 mm);  
15 placebo segments of Stamylex® 9119 (8.5 mm).

(f) first compartment of material of entry 7 (110 mm);  
second compartment of material of entry 13 (17 mm);  
placebo segments of Stamylex® 9119 (13 mm).

20 (g) first compartment of material of entry 6 (110 mm);  
second compartment of material of entry 22 (20 mm);  
placebo segments of Stamylex® 9119 (13.5 mm).

25 (h) first compartment of material of entry 7 (110 mm);  
second compartment of material of entry 22 (21 mm);  
placebo segments of Stamylex® 9119 (13 mm).

(i) first compartment of material of entry 6 (110 mm);  
30 second compartment of material of entry 22 (24 mm);  
placebo segments of Stamylex® 9119 (8.5 mm).

(j) first compartment of material of entry 6 (110 mm);  
second compartment of material of entry 23 (21 mm);  
placebo segments of Stamylex® 9119 (12 mm).

5 (k) first compartment of material of entry 6 (110 mm);  
second compartment of material of entry 24 (21 mm);  
placebo segments of Stamylex® 9119 (12 mm).

10

**Example 4**

A vaginal ring is composed from two steroid loaded compartments having the following composition and dimensions (see Figures):

15 **first compartment (Fig. 2)**  
a three-layered fibre comprising:  
core (1): Evatane® 1040 VN4; diameter 2.96 mm ; middle layer (2) loaded with 15 % w/w of etonogestrel in Evatane® 28-25; thickness 75  $\mu$ m, extruded at 105 °C; outer layer (3): Evatane® 1040 VN4; thickness 195  $\mu$ m.

20 The steroid loaded mixture and Evatane® 1040 VN4 are co-extruded at 120 °C to form a trilayer fibre.  
**second compartment (Fig. 3)**  
a two-layered fibre comprising:  
core (4): Evatane® 28-25 loaded with 0.25 % w/w of etonogestrel and 0.75 % w/w of ethinyl  
25 estradiol (EE); diameter 3.35 mm, extruded at 105 °C; outer layer (5): Evatane® 1020 VN3; thickness 145  $\mu$ m.  
The steroid loaded mixture and Evatane® 1020 VN3 are co-extruded at 110 °C to form a skin-core fibre.  
The trilayer fibre is cut into fibre pieces of 110 mm and the skin-core fibre is cut into fibre  
30 pieces of 47 mm. One small and one large fibre piece are joined together to a ring-shaped device by hot-gas welding technique.

## Example 5

The following first compartments containing etonogestrel were prepared. The medicated layer material is Evatane 28-25; the skin/core material is Evatane 1040 VN4 (outer diameter is 3.5 mm).

Entry	Medicated layer load (% w/w)	Skin thickness (μm)	Medicated layer thickness (μm)	Extrusion temp. (°C)
25	15	175	75	120
26	15	140	75	120
27	15	220	75	120

The following second compartments containing etonogestrel and ethinyl estradiol (EE) were prepared. The medicated layer material is Evatane 28-25; the skin material is Evatane 1020 VN3 (outer diameter is 3.5 mm).

Entry	medicated layer load		skin thickness (μm)	extrusion temp. (°C)
	Etonogestrel (% w/w)	EE (% w/w)		
28	0.25	0.75	85	110
29	0.25	0.75	125	110
30	0.25	0.75	145	110
31	0.30	0.90	175	110
32	0.20	0.60	115	110
33	0.15	0.45	145	110

The following vaginal rings were prepared according to the method of Example 4:

- 5        a) First compartment of material of entry 2 (110 mm)  
              second compartment of material of entry 31 (47 mm)
  
- 10      b) First compartment of material of entry 2 (110 mm)  
              second compartment of material of entry 32 (47 mm)
  
- 15      c) First compartment of material of entry 25 (100 mm)  
              second compartment of material of entry 30 (50 mm)
  
- 20      d) First compartment of material of entry 6 (110 mm)  
              second compartment of material of entry 30 (47 mm)
  
- 25      e) First compartment of material of entry 7 (110 mm)  
              second compartment of material of entry 29 (40 mm)
  
- 30      f) First compartment of material of entry 26 (80 mm)  
              second compartment of material of entry 33 (75 mm)
  
- 35      g) First compartment of material of entry 27 (125 mm)  
              second compartment of material of entry 28 (30 mm)

## Claims:

1. A ring-shaped device comprising
  - (a) a first compartment comprising a non-medicated core of ethylene-vinylacetate copolymer, encircled by a steroid hormone loaded ethylene-vinylacetate copolymer middle layer, and a non-medicated outer layer of ethylene-vinylacetate copolymer;
  - (b) a second compartment comprising a core of ethylene-vinylacetate copolymer loaded with a steroid hormone and a non-medicated outer layer of ethylene-vinylacetate copolymer; and
  - (c) optionally placebo segments of a thermo-plastic material separating the first from the second compartment.
2. The ring-shaped device of claim 1, wherein the steroid hormone of the middle layer of the first compartment is a progestogen, and the ethylene-vinylacetate copolymer core of the second compartment is loaded with a mixture of a progestogen and an estrogen.
3. The ring-shaped device of claim 2, wherein the ethylene-vinylacetate copolymer middle layer of the first compartment is saturated with the progestogen, and the ethylene-vinylacetate copolymer core of the second compartment is loaded with a sub-saturated mixture of the progestogen and the estrogen.
4. The ring-shaped device of claim 3, wherein the ethylene-vinylacetate copolymer middle layer of the first compartment comprises crystalline progestogen.
- 25 5. The ring-shaped device of any one of claims 1-4, wherein the lengths of the first and second compartment have a ratio of between 15:1 and 1:1, and preferably of about 2:1, and wherein the lengths of the placebo segments, if present, are long enough to prevent excessive mixing of the progestogen of the first compartment with the progestogen and/or estrogen of the second compartment, being preferably about at least half of the length of the second compartment.

6. The ring-shaped device of any one of claims 1-5, wherein the ring diameter is about 53.5 mm, the cross sectional diameter is about 3.5 mm, the length of the first compartment is about 100 to 110 mm, the length of the second compartment is about 10-40 mm, and each of the two placebo segments has a length of about 5 to 20 mm, or the length of the second compartment is about 42-52 mm when the placebo segments are not present.  
5
7. The ring-shaped device of any one of claims 1-6, wherein the thermo-plastic material of the placebo segments, if present, is high density polyethylene.
- 10 8. The ring-shaped device of any one of claims 1-7, wherein the progestogen is etonogestrel and the estrogen is ethinyl estradiol.
- 15 9. The ring-shaped device of claim 8, wherein the ethylene-vinylacetate copolymer layer of the first compartment is loaded with about 15 % w/w of etonogestrel, and the ethylene-vinylacetate copolymer core of the second compartment is loaded with about 0.25 to 0.5 % w/w of etonogestrel and about 0.75 to 1.5 % w/w of ethinyl estradiol.
- 20 10. A method of manufacture of the ring-shaped device of any one of claims 1-9, comprising co-extrusion of the core and the layer(s) of each of the first and second compartments into a fibre, after which suitable pieces of each fibre are assembled to the ring-shaped device by melting the pieces to the thermo-plastic material of the placebo segments in a mould.
- 25 11. A method of manufacture of the ring-shaped device of any one of claims 1-9, comprising welding technique whereby the first compartment is attached to the second compartments into the ring-shaped device.

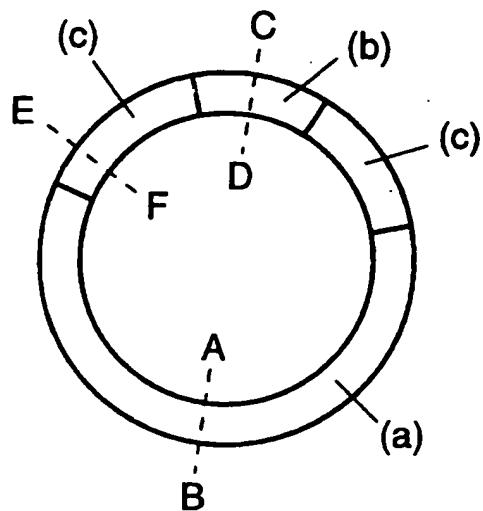


Fig. 1

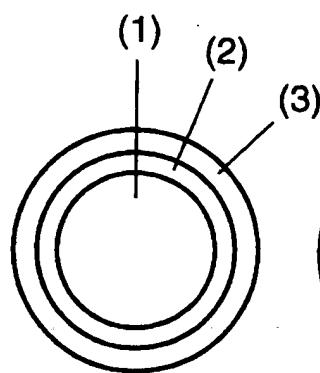


Fig. 2

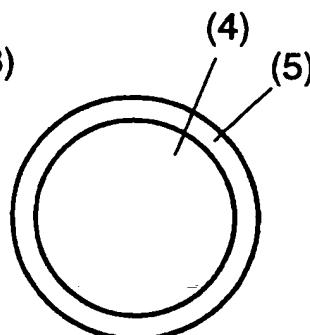


Fig. 3

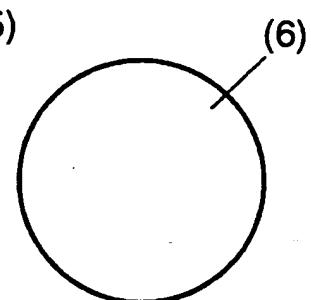


Fig. 4

**INTERNATIONAL SEARCH REPORT**

1. National Application No  
PCT/EP 96/02935

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR,A,2 347 053 (SCHERING AG) 4 November 1977 see claims see figures see page 5, line 33 - page 6, line 7 see example 1 ---	1-11
A	EP,A,0 050 867 (SCHERING AG) 5 May 1982 cited in the application see claims see figure 1 ---	1-11
A	US,A,4 237 885 (P.S.L.WONG ET AL.) 9 December 1980 cited in the application see the whole document ---	1-11 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

Date of mailing of the international search report

9 October 1996

15.10.96

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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 96/02935

## C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 292 965 (H.A.NASH ET AL.) 6 October 1981 cited in the application see claims see figure 1 ---	1-11
A	US,A,4 596 576 (H. DE NIJS) 24 June 1986 cited in the application see the whole document -----	1-11

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**INTERNATIONAL SEARCH REPORT**

Information on patent family members

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PCT/EP 96/02935

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